REVIEW

Best practice in primary care pathology: review 7

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This seventh best-practice review examines four series of common primary care questions in laboratory medicine: (1) blood count abnormalities 2; (2) cardiac troponins; (3) high-density lipoprotein cholesterol; and (4) viral diseases 2. The review is presented in a question–answer format, with authorship attributed for each question series. The recommendations are a précis of guidance found using a standardised literature search of national and international guidance notes, consensus statements, health policy documents and evidence-based medicine reviews, supplemented by Medline Embase searches to identify relevant primary research documents. The recommendations are not standards, but form a guide to be set in the clinical context. Most are consensus based rather than evidence based. They will be updated periodically to take account of new information.

This is the seventh in a planned series of reviews to answer a number of questions that arise in primary care pathology.

Each topic is introduced with a brief summary of the type of information found and is handled separately, with authorship attributed.

Although the individual topics are not related—they cover the disciplines of clinical biochemistry, microbiology, immunology, haematology and cellular pathology—they are designed to form a resource that, once completed, will be indexed and will cover a wide range of the most common primary care laboratory issues, to be made available to users.

In instances where the new UK General Medical Services (GMS) contracts make specific reference to a laboratory test, the indicator or target is appended at the end of the answer.

BLOOD COUNT ABNORMALITIES 2 (MJG, DB, WSAS, GS, PJC)

This second series of blood count scenarios examines selected abnormalities of white cell counts—namely, lymphocytosis, neutropenia and eosinophilia.

As a typical full blood count report may contain ⩾10 results, values outside the quoted reference ranges occur frequently on a statistical basis. These questions and answers attempt to establish thresholds for clinical action or referral and identify situations that are likely to be of clinical importance. Some (eg, lymphocytosis) are extensively reviewed in existing guidelines, cited as the primary reference sources, whereas others, such as eosinophilia, draw guidance mostly from extrapolation from observational studies

When should I refer an adult patient with a lymphocytosis?

We recommend the following criteria for referral:

- a lymphocytosis ($>5.0\times10^9$ cells/l), that is not explained clinically by acute, self-limiting viral illness.
- high lymphocyte count in patients previously diagnosed as having stage A chronic lymphocytic leukaemia (CLL) and followed up in primary care, if accompanied by anaemia and/or thrombocytopenia.
- development of any indications for treatment in a patient with grade A CLL being followed up in primary care.

The primary aim of this answer is to establish the need for referral of patients with possible leukaemia or lymphoma. Patients may be found to have a lymphocytosis in the course of routine investigations for unrelated symptoms or as part of health screening. The cause may be an increase in T lymphocytes that is often reactive to an acute illness and is rarely a reflection of malignancy.[1] Alternatively, a B cell lymphocytosis may be present, which may be polyclonal but more often is the result of a clonal lymphoproliferative disorder, usually CLL. Other conditions presenting with a lymphocytosis, such as follicular lymphoma, marginal zone lymphoma, mantle-cell lymphoma or hairy-cell leukaemia, will often have clinical features, such as anaemia, splenomegaly or lymphadenopathy, and the blood film appearances may not be compatible with CLL.[1] Although there is limited clear guidance, it would seem reasonable to wait for an acute viral illness to resolve and recheck the lymphocyte count when a lymphocytosis is associated with features of acute viral illness.

Diagnosis

A definitive diagnosis of CLL is based on the combination of a lymphocytosis $>5.0\times10^9$ cells/l and a characteristic lymphocyte morphology and immunophenotype. Immunophenotyping is required to accurately classify the nature of the

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Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; EBV, Epstein–Barr virus; FBC, full blood count; GMS, General Medical Services; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

lymphocyte proliferation, thus enabling an appropriate treatment plan to be made. Although some morphological features are associated with the different types of lymphocyte proliferation, these are no longer acceptable as the only means of confirming the diagnosis that will influence the patient's management. Immunophenotyping is always indicated in patients requiring treatment, in patients with lymphocytosis, that on morphological review is not typical of CLL, and in patients in whom it is thought important to exclude a reactive lymphocytosis.[1] Blood films should be prepared for patients who have lymphocytosis $>5\times10^9$ cells/l when reviewed for the first time.[2]

When should I refer a patient with lymphocytosis to a haematologist?

Patients with lymphocytosis should be referred for a review by a haematologist if they have lymphadenopathy, splenomegaly, anaemia, thrombocytopenia, or when the blood film reports a lymphocytosis that is not consistent with CLL,[1] or when the lymphocytosis is not explained clinically by an acute self-limiting viral illness (box 1).

Clinical follow-up of a patient with grade A CLL

The management of patients with early (stage A) CLL requires a collaborative approach between primary and secondary care. Some patients in stage A are regarded as having ''smouldering CLL'', characterised by haemoglobin >13 g/dl, lymphocyte count $<30\times10^9$ cells/l, minimal or no lymphadenopathy and a lymphocyte doubling time >12 months, and these patients have a low progression rate (15% at 5 years, 80% 10-year survival). By contrast, patients with stage B or C disease have a 40% 5-year survival and require early treatment.[3]

By extrapolation from the guidelines of the British Committee for Standards in Haematology,[1] patients with indolent stage A CLL could be monitored in the primary care setting with a FBC every 6 months for the first 2 years. If the lymphocyte count doubles during this time, then the patient should be referred to a haematologist for an assessment. For patients whose lymphocyte count remains stable for this time, there is a low likelihood of the disease progressing, and monitoring can be reduced to an annual FBC. The follow-up of the patients seen initially in hospital who do not require treatment may be organised in primary care, in hospital outpatients or through a home-care service, depending on local resources and patient wishes. Before patients are discharged from the hospital follow-up, a clear management plan should be documented, which should include criteria for re-referral to the haematology service.

UK GMS contract indicator: none.

When should I refer a patient with a low neutrophil count?

Neutropenia is potentially associated with life-threatening infection and we recommend that the following situations are of significance and require referral to secondary care:

Neutrophils $<1\times10^9$ cells/l and the patient is unwell/febrile: (especially if undergoing cancer chemotherapy): refer urgently for admission.

Neutrophils $<1\times10^9$ cells/l and the patient is well/afebrile: repeat FBC with blood film examination within 48 h; if neutropenia persists, refer for urgent haematology outpatient department appointment.

Neutrophils $1–1.5\times10^9$ cells/l and the patient is well: refer to haematology or discuss with haematologist if neutropenia is progressively severe or persists on two occasions at least 6 weeks apart; or refer to haematology or discuss with haematologist if other blood count abnormality is present and persistent on two occasions at least 6 weeks apart.

Neutropenia is classified as

- mild $1.0–1.5\times10^9$ cells/l
- moderate $0.5–1.0\times10^9$ cells/l
- severe $<0.5\times10^9$ cells/l.[4]

Patients with neutrophil count $<1\times10^9$ cells/l and fever require urgent, parenteral, broad-spectrum antibiotics, as infection may rapidly progress to established septic shock.

We found no published guidance for referral of patients with mild neutropenia. This guidance is drawn from a consensus of author and reviewer opinion.

Benign ethnic neutropenia is relatively common in individuals of African descent (neutrophil counts down to 1×10^9 cells/l) and is also seen in some of Middle Eastern extraction. Individuals are physically normal and lack a history of susceptibility to infection. Confirm neutropenia with repeat FBC and confirm normal morphology with blood film.[4]

Transient neutropenia not lasting >2 weeks is usually related to viral infections and not associated with clinical problems.[5] Occasionally, these infections may contribute to mild neutropenia for several months after the illness.

Most severe neutropenias are associated with fever, oral ulceration, and bacterial or fungal infections.[6 7] The following areas should be reviewed:

History: Frequency and severity of infections, mouth ulcers, recent viral illness, exposure to drugs and toxins, and symptoms of malabsorption.[4]

Drugs: Excluding cancer chemotherapy, the highest-risk categories are antithyroid drugs, trimethoprim–sulfamethoxazole, sulfasalazine and neuropsychotropics. Many drugs may cause a chronic mild neutropenia—for example, non-steroidal anti-inflammatory drugs, sodium valproate (box 2).

Examination: Notably mouth ulcers, fever, signs of infection.

Investigations: Notably whether the full blood count is otherwise normal.

Recurrent fever and oral ulcerations can be due to cyclical neutropenia[8]: a rare autosomal dominant disorder in which neutrophil counts oscillate between 0.1×10^9 and 1.5×10^9 cells/l every 21 days. Neutropenic periods last 3–6 days, accompanied by malaise, anorexia, fever, lymphadenopathy and mucosal ulceration. The diagnosis is established by obtaining neutrophil counts twice weekly for a minimum of 6 weeks, but this should not hinder referral of severe neutropenia to secondary care.[7]

UK GMS contract indicator: none.

How should I interpret a raised eosinophil count?

We recommend the following if a patient's eosinophil count is (persistently) $>0.35\times10^9$ cells/l or $>1.5\times10^9$ cells/l:

Clinical history concentrating on allergy/atopy, gastrointestinal, skin, respiratory and joint symptoms, and any change in general health (malignancy) combined, depending on clinical context, with:

- blood film (to examine for any morphological abnormality of the eosinophils),
- stool parasite examination
- urine analysis.

Non-specific allergy testing is not recommended

The upper limit of the reference range for the eosinophil count is $>0.35\times10^9$ cells/l.[10] Eosinophilia has been subdivided into mild (0.35–1.5), moderate (1.5–5) and severe $(>5)\times10^6$ cells/l.[11] In a review of 1862 cases studied in an Italian series,[12] the most common causes and frequencies

Box 1: Indications for treatment in chronic lymphocytic leukaemia[1]

Progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- Massive (>10 cm) or progressive lymphadenopathy
- Massive (>6 cm) or progressive splenomegaly
- Progressive lymphocytosis
- >50% increase over 2 months
- Lymphocyte doubling time <6 months
- Systemic symptoms (It is important to exclude other causes for these symptoms such as infection)
- Weight loss >10% in previous 6 months
- Fever >38°C for ⩾2 weeks
- Extreme fatigue
- Night sweats
- Autoimmune cytopenias

(which include potential drug reactions in several categories) can be summarised as follows:

- atopic diseases including asthma 79.7%
- parasitic infections 8.2%
- haematological neoplasia 2.4%
- allergic/atopic skin diseases 2.1%
- solid tumours 1.9%
- gastrointestinal disease 1.6% (mostly inflammatory bowel disease and coeliac disease)
- lung disease 0.8%
- connective tissue diseases 0.6%.

These patients were identified from detailed clinical history, and an escalating and extensive series of investigations were performed until a diagnosis was established. A further 2.7% of patients were defined as having eosinophilia of unknown significance.

An additional group of patients has been identified with idiopathic hypereosinophilic syndrome,[13] which by definition excludes all patients with eosinophilia for which a cause can be found.[14] A North American study of incidental eosinophilia[15] (defined as eosinophil count of >5% or $>0.7\times10^9$ cells/l in this study) in 195 300 automated haematology profiles found that of the 225 cases (0.1% of samples), almost all were attributable to either allergic processes or to known underlying diseases (advanced malignancy, connective tissues disease). Only two cases (patients receiving gold therapy) were both unanticipated and not associated with signs or symptoms of the cause of the eosinophilia. In 30% of cases, no cause was found by the patient's doctor, although these patients were not subject to the same escalating investigations as in Rothenberg's report.[11] The authors concluded that repeat blood count and focused investigations (parasitology, skin prick testing depending on clinical context, foreign travel) are sufficient, and that extensive diagnostic testing is unnecessary. Although the great majority of cases will be attributable to common allergic or parasitic disease, a small proportion potentially reflect other serious lung, gastrointestinal, renal autoimmune or malignant disease, although these would be expected to exhibit other signs or symptoms of the disease. In addition, a small number of patients will present with either the hypereosinophilia syndrome or a haematological malignancy in which the only feature may be eosinophilia. Therefore, it would be reasonable to recommend that patients with persistent (>6 months) mild eosinophilia or a finding of moderate or increasing eosinophilia in which the above investigations do not reveal a cause should be referred for immediate assessment. In patients with moderate eosinophilia, if any signs of organ damage are present, as indicated by cardiac or pulmonary symptoms, then the referral should also not be delayed.

UK GMS contract indicator: none.

Box 2: Drugs and chemicals associated with neutropenia, excluding cytotoxic chemotherapy (adapted from Moses[9])

- Antimicrobials include penicillin, cephalosporins, vancomycin, chloramphenicol, gentamycin, clindamycin, doxycycline, flucytosine, nitrofurantoin, novobiocin, minocycline, griseofulvin, lincomycin, metronidazole, rifampin, isoniazid, streptomycin, thiacetazone, mebendazole, pyrimethamine, levamisole, ristocetin, sulfonamides, chloroquine, hydroxychloroquine, quinacrine, ethambutol, dapsone, ciprofloxacin, trimethoprim, imipenem/cilastatin, zidovudine, fludarabine, acyclovir and terbinafine.
- Analgesics and anti-inflammatory agents include aminopyrine, dipyrone, phenylbutazone, indomethacin, ibuprofen, acetylsalicylic acid, diflunisal, sulindac, tolmetin, benoxaprofen, barbiturates, mesalazine and quinine.
- Antipsychotics, antidepressants and neuropharmacological agents include phenothiazines (chlorpromazine, methylpromazine, mepazine, thioridazine, prochlorperazine, trifluoperazine, trimeprazine), clozapine, risperidone, imipramine, desipramine, diazepam, chlordiazepoxide, amoxapine, meprobamate, thiothixene and haloperidol.
- Anticonvulsants include valproic acid, phenytoin, trimethadione, Mesantoin, ethosuximide and carbamazepine.
- Antithyroid drugs include thiouracil, propylthiouracil, methimazole, carbimazole, potassium perchlorate and thiocyanate.
- Cardiovascular drugs include procainamide, captopril, aprindine, propranolol, hydralazine, methyldopa, quinidine, diazoxide, nifedipine, propafenone, ticlopidine and vesnarinone.
- Antihistamines include cimetidine, ranitidine, tripelennamine (Pyribenzamine), methaphenilene, thenalidine, brompheniramine and mianserin.
- Miscellaneous drugs include allopurinol, colchicine, aminoglutethimide, famotidine, bezafibrate, flutamide, tamoxifen, penicillamine, retinoic acid, metoclopramide, phenindione, dinitrophenol, ethacrynic acid, dichlorodiphenyltrichloroethane, cinchophen, antimony, pyrithyldione, rauwolfia, ethanol, chlorpropamide, tolbutamide, thiazides, spironolactone, methazolamide, acetazolamide, intravenous immunoglobulin and levodopa.
- Heavy metals include gold, arsenic and mercury.

CARDIAC TROPONINS (POC AND RM)

Cardiac troponins are replacing conventional markers of myocardial injury (creatine kinase and its isoenzymes, and aspartate transaminase) as sensitive and specific markers of injury. This answer examines the specific situation of patients presenting to a general practitioner with chest pain, and not the

emergency-care hospital setting, and attempts to provide guidance on when, if ever, this test may be appropriate in this situation. Detailed guidance has been produced in the recent NHS [National Health Service] Quality Improvement Scotland Health Technology Assessment,[16] which is used as the primary reference source.

When should I measure cardiac troponin in someone who comes to the surgery with chest pain?

We recommend that serum troponin should not be measured in primary care, except in the following possible situations:

- when admission to hospital would not be considered for other medical reasons
- if a patient presents after a single episode of chest pain 24–72 h previously, in order to establish whether myocardial damage has occurred.

Myocardial infarction, or the acute coronary syndrome is a clinical diagnosis, and measurement of cardiac troponin in serum, although sensitive and specific for ACS, is only part of that diagnosis.

Troponin is a component of the myocardial tissue that acts as a molecular switch to regulate muscle contraction. Two troponins of clinical interest, cardiac troponin T and cardiac troponin I, are found only in the myocardium.[17]

Release of cardiac troponin T occurs on cardiac damage. Measurement of cardiac troponin is the definitive biochemical test for detection of myocardial infarction.[18]

Recent recommendations from the European Society of Cardiology and the American College of Cardiology for the definition of myocardial infarction stipulate that there must be a rise and fall in troponin accompanied by either clinical features suggestive of cardiac disease or changes in the ECG.[18]

Patients with recent (within 24 h) or recurrent acute chest pain, that might be cardiac in nature will normally require immediate emergency assessment. If the patient has episodes of chest pain on exertion only, referral to a rapid-access chest pain clinic may be considered more appropriate.

The only exception, where troponin measurement might be considered, is if the patient has other medical problems that mean that they would not wish to be sent to hospital. In this case, measurement of cardiac troponin and an ECG 24 h after the acute event can be used to confirm or exclude whether the patient has had an ACS.

If a patient presents with a single episode of chest pain 24–72 h previously, measurement of cardiac troponin and an ECG will establish whether or not the chest pain was due to an ACS. If the patient has had a myocardial infarction, he or she should be referred urgently for cardiac review and for further investigation. Whereas paradigms for care of patients with ACS may change, the recent National Health Service Quality Improvement Scotland Health Technology Assessment refers to troponin testing only in the context of hospital care, and not in a primary care setting.[16]

Any cause of cardiac damage, such as trauma (eg, traffic accident, stabbing) myocarditis, or renal failure (where cardiac death is common) will also result in increased troponin. Many of secondary causes of cardiac damage have been observed that can cause a troponin rise.[19] In these situations, such rises are associated with worse outcome.[19]

Some skeletal myopathies have cardiac as well as skeletal muscle involvement. Measurement of cardiac troponin will detect this. If creatine kinase is persistently increased in a patient, measurement of cardiac troponin will establish whether this has a cardiac component.

UK GMS contract indicator: none.

HIGH-DENSITY LIPOPROTEIN MEASUREMENT AND TREATMENT

The high-density lipoprotein cholesterol (HDL-C) level is inversely related to coronary risk, and is a necessary measurement for the use of coronary risk calculation tables and programs. Until recently, the emphasis on treatment targets has been predicated on low-density lipoprotein cholesterol (LDL-C) targets, although recent guidelines have highlighted the need to consider intervening when HDL-C is low. These question-and-answer sets examine indications for measuring HDL-C, and consider when intervention may be appropriate.

This guidance should be read in conjunction with reviews 1 and 3 of this series, which consider monitoring other aspects of cholesterol and triglyceride measurement,[20 21] which are accompanied by a further discussion in a case study on lipids in a series of articles in the *BMJ*.[22]

When and how often should HDL-C be measured together with total cholesterol and LDL-C?

We recommend that when assessing cardiovascular risk:

- HDL-C should be measured with total cholesterol, triglycerides and LDL-C (an initial non-fasting sample is acceptable).
- If the non-fasting total cholestrol/HDL-C ratio is raised or the patient is at high risk (>20% 10-year coronary heart disease (CHD) risk), a fasting lipid profile should be obtained.
- Adult patients with diabetes should have an annual lipid profile, including HDL-C level.

In patients receiving lipid-lowering treatment, HDL-C should be measured:

- 8 ($\pm$4) weeks after starting or changing any intervention to raise HDL-C (lifestyle modification with or without drugs)
- annually thereafter in all patients receiving lipid-lowering treatment.

Or as a minimum:

- Annually in patients with HDL-C <1.3 or >1.7 mmol/l.

Large population studies have consistently demonstrated a strong inverse relationship between plasma HDL-C and the risk of CHD.

Low HDL-C levels may have a genetic cause and are also associated with increased triglycerides, obesity and high carbohydrate intakes (>60% of calories), physical inactivity, type 2 diabetes, cigarette smoking and the use of certain drugs (eg, β blockers, anabolic steroids and progestogens).[23]

Studies and drugs available to examine the benefit of specifically treating low HDL-C levels in isolation are lacking. Most treatment recommendations are aimed at achieving target LDL-C levels for which there is convincing evidence of benefit.

Recent American[24] and British[25 26] guidelines do not include specific recommendations on thresholds for initiating drug treatment, on treatment goals and on monitoring intervals for people with low HDL-C levels and varying levels of cardiovascular risk, but make reference to the need for practitioners to be aware of the increased risk associated with low HDL in their treatment decisions.

Screening

Measurement of HDL is essential to accurately assess absolute cardiac risk and is necessary for the risk assessments recommended by the UK National Service Framework[26] and Joint British Societies.[25]

HDL-C in the non-fasting state is lower by 5%–10% than in the fasting state. Non-fasting measurements, therefore, slightly overestimate CHD risk but are regarded as sufficiently accurate

to use in screening and are more convenient for patients.[27] All people with abnormal non-fasting screening lipids or at high risk should have a fasting lipid profile.[25 26]

The National Institute for Health and Clinical Excellence recommends that all people with diabetes should have an annual lipid profile (but makes no recommendations on the management of low HDL-C).[28]

Monitoring interventions to raise HDL-C

No clear guidance is available on this topic. As any intervention to raise HDL-C will normally run concurrently with other lipid management, we recommend that HDL-C levels for people undertaking interventions to raise HDL-C levels be maintained at the same intervals as for people who are receiving treatment to lower cholesterol and/or triglycerides—that is, 8 ($\pm$4) weeks after starting treatment and then every 8 ($\pm$4) weeks until on target.

Annual monitoring of patients receving lipid-lowering treatment

The Joint British Societies' guideline[25] recommends that a full lipid profile (ie, total cholesterol, HDL, triglyceride and measured or calculated LDL-C) be performed annually in patients receving lipid-lowering treatment. It could be argued that repeated measurement of HDL-C is of limited benefit in those in whom specific intervention would be intended, if the total cholesterol adequately acts as a surrogate marker for LDL-C. As a minimum, we would therefore suggest measurement of HDL-C in patients in whom the total cholesterol figure may be an inaccurate surrogate for LDL-C(see Smellie *et al*[21] for a brief review of calculated LDL-C) or in whom HDL-raising methods might be considered. In the absence of specific guidance, this is set arbitrarily at $\leqslant$1.2 (the potential intervention threshold in women) and $\geqslant$1.7 (when the LDL may be lower than expected as indicated by total cholesterol).

UK GMS contract indicator: none.

What is a low HDL-C and how can it be treated?

We recommend:

Low HDL can be considered as $<$1.0 mmol/l in men and $<$1.2 mmol/l in women.

Modification:

- Lifestyle modification as the first approach.
- Drug treatment to raise HDL-C levels may be considered, once the target/lowest achievable LDL-C is reached, in secondary and high-risk primary prevention (those whose 10-year cardiovascular risk exceeds 20%) if HDL-C remains low despite lifestyle interventions.

Evidence suggests that the following lifestyle modifications raise HDL-C levels, although there is limited clinical endpoint evidence that can be related specifically to HDL-C:

- regular, brisk aerobic exercise for 30 min most days of the week
- cessation of smoking
- weight loss for overweight and obese people
- moderate alcohol intake
- a diet rich in n-3 polyunsaturated fatty acids (oils, nuts, cold-water fish and shellfish) with limited carbohydrates that have a high glycaemic load.

A recent meta-analysis looking at the efficacy and safety of HDL-C-increasing compounds (53 trials involving 16 802 people using fibrates and 30 trials involving 4749 people using niacin) found that apart from flushes in the niacin group, both fibrates and niacin were shown to be effective in increasing HDL-C levels, well tolerated and safe,[29] although the recent field study did not show a large sustained increase in HDL-C.[30] Prospective epidemiological studies have shown that an increase in HDL-C of 0.1 mmol/l reduces the relative risk of a coronary event by 2% in men and 3% in women.[31]

Most lipid management studies, however, have focused on reducing LDL-C rather than raising HDL-C levels. A recently published cohort study (18 815 people) estimated the effect of changes in HDL-C adjusted for changes in total cholesterol on cardiovascular events.[32] It found that a rise in HDL-C by $>$20% reduced the risk of a cardiovascular event in people taking lipid-lowering treatment or who had been hospitalised previously for cardiovascular disease (risk ratio (RR) 0.6; 95% CI 0.44 to 0.83). However, it found no statistical relationship between HDL change and cardiovascular outcome in people who had not been hospitalised previously, or who were not taking lipid-lowering treatment.

The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)[2] recommends that a low HDL-C ($<$1.0 mmol/l) should receive clinical attention, but does not recommend a specific treatment goal.

The National Service Framework[26] and National Institute for Health and Clinical Excellence[28] guidelines make no specific recommendations on the management of HDL-C, although the recent Joint British Societies guideline refers to the need to address other lipid abnormalities, including low HDL ($<$1.0 mmol/l in men and 1.2 mmol/l in women).[25]

The Expert Group on HDL-C[31] recommended a treatment goal of $\geqslant$1.0 mmol/l for people with cardiovascular disease and those without cardiovascular disease but at high risk, especially those with type 2 diabetes or the metabolic syndrome.

Prescribers should be aware of the increased risk of myopathy and rhabdomyolysis in patients treated with fibrate–statin combinations, although absolute risk is low. Specialist advice is recommended before combination treatment in people who are (because of hypothyroidism, alcohol misuse, existing myopathy).[20]

A recent consensus statement has also supported the combined use of statin–nicotinic acid preparations as a useful strategy to reduce CHD risk in patients with diabetes and the metabolic syndrome.[33]

UK GMS contract indicator: none.

VIRAL DISEASES 2 (WI, WSAS, KGK)

These two questions consider the separate subjects of infectious mononucleosis and rash in pregnancy. The first is complicated by the availability of different tests, typically in two laboratory disciplines (haematology and virology), and attempts to guide the respective use of the tests in different clinical contexts. The second has already been extensively researched in standard operating procedures produced by the Health Protection Agency Evaluations and Standards Laboratory, London, UK, and restates much of the content of these. These standard operating procedures are issued by the Standards Unit, Evaluations and Standards Laboratory, Centre for Infections, Health Protection Agency and are endorsed by the Health Protection Unit (UK), the UK NHS, the National Public Health Service for Wales, the UK Clinical Virology Network, the Association of Medical Microbiologists, the UK Institute of Biomedical Scientists, the Association of Clinical Microbiologists, the Scottish Microbiology Association and the Welsh Microbiological Association.

When should I investigate a patient for possible infectious mononucleosis due to Epstein–Barr virus?

We recommend testing:

- in febrile patients aged between 10 and 30 years with sore throat, fatigue and splenomegaly, palatal petechiae, or posterior cervical, axillary or inguinal lymphadenopathy[34]
- in younger or older patients:
- as an adjunct to the investigation of acutely raised transaminases or haemolytic anaemia
- if infectious mononucleosis is strongly suspected clinically or from contact history.

The term infectious mononucleosis is a syndromic diagnosis, which can arise through a number of different aetiologies. The most common cause is primary infection with Epstein–Barr virus (EBV), but a clinically indistinguishable illness may arise through primary cytomegalovirus (CMV), human herpesvirus-6 or toxoplasmosis infection. In addition, the acute seroconversion illness after recent acquisition of HIV infection may bear many similarities to infectious mononucleosis, and is often described as a ''glandular-fever-like illness''.

Infectious mononucleosis is common in the 10–30-year age band (6–8 per 1000 per year or higher in communities of adolescents and young adults).[35] It is rarer under the age of 10 years or over 30 years (<1 case per 1000 per year). Adults are more likely to present with a hepatitic picture.[36]

No evidence-based guidelines were found and our recommendations are summarised from a recent review,[35] supported by an earlier cohort study based on the at-risk population and prevalence of symptoms.[37 38]

As the treatment of infectious mononucleosis is symptomatic and the only direct management recommendation is avoidance of contact sports,[39] the main reason for investigating patients would seem to be to confirm the cause of symptoms and exclude other, more serious diseases, except in administrative situations (eg, loss of work) if a specific diagnosis is desired.

The American Family Physician review[35] also recommends testing for group A β-haemolytic streptococcus concomitantly in the above group of patients with febrile pharyngitis and lymphadenopathy. This will be considered in a future question.

UK GMS contract indicator: none.

What tests should I use to investigate a patient for possible infectious mononucleosis?
We recommend:

- FBC and differential count for lymphocytosis and atypical lymphocytes
- heterophile antibodies (Monospot or similar) in immunocompetent adults
- Viral serology in children <12 years of age[40 41] and in the immunocompromised.

If a first heterophile antibody/FBC test is negative/not supportive of infectious mononucleosis due to EBV:

- repeat test for heterophile antibodies in 5–7 days
- consider specific EBV viral serology (viral capsid antigen) if rapid rule-out needed (eg, urgent return to sports desired).

If a second heterophile antibody test is negative and confirmation of diagnosis is considered clinically important:

- Testing for CMV and toxoplasmosis is specifically recommended only for pregnant women and in the immunocompromised
- Testing for HIV is recommended in at-risk patients.

The rigorous combined clinical and laboratory criteria defined by Hoagland[36] seem to be the most specific for infectious mononucleosis but seem to lack sensitivity in clinical practice.[35] A positive result for heterophile antibody or >20% atypical lymphocytes or >10% atypical lymphocytes with lymphocyte count >50% of differential are considered strong evidence of infectious mononucleosis, and no further testing is recommended in an American review.[35] However, false-negative rates may be 25% in week one of infection, falling to approximately 5% in week three,[36] and repeat testing is recommended in suspected cases if an initial test is negative. False-negative rates are also reported to be higher in children,[40] in whom specific antibody testing is recommended,[41] and in the immunocompromised, in whom immunological testing is considered potentially unreliable.[41] The same UK guidance[41] also recommends EBV-specific serology as preferable to heterophile antibodies, although it describes the latter as acceptable under (unspecified) clinical circumstances. Our recommendation attempts to reconcile the UK and American Family Physician recommendations for uncomplicated cases in primary care.

Haematological complications, if present (eg, neutropenia, haemolytic anaemia), will become apparent from the results of the FBC, and will prompt further investigation by the performing laboratory as indicated.

Specific antibodies to EBV viral capsid antigen are considered better than heterophile antibodies in ruling out EBV infectious mononucleosis, and are similar in their ability to rule in infection[42]; they are recommended for use in patients with typical symptoms and negative results for heterophile antibodies, or where rapid rule-out is required (eg, for patients wishing to return to sports). They develop slightly earlier than heterophile antibodies. A negative result for IgM antibodies to viral capsid antigen is considered strong evidence against infectious mononucleosis. The IgM antibody is more specific for acute infection and recommended as the test of choice in the American Family Physician review.[35] The IgG antibody persists after infection. Specific testing strategies may vary between laboratories, as no recommended standard was found. Antibodies to the EBV nuclear antigen typically develop after 6–8 weeks and can be used to identify past, and, therefore, non-acute, infection. Conversely, negative EBV nuclear antigen with positive capsid IgM is suggestive of acute infection.

Other infections, such as acute CMV disease and toxoplasmosis, can produce clinical manifestations similar to EBV infectious mononucleosis and may also be associated with positive heterophile antibody tests. Nevertheless, it is unclear whether there is any advantage in testing serologically for these other infections except in the pregnant woman or in the immunocompromised, as these diseases are usually self-limiting and resolve with supportive therapy only. Specific guidance on when to investigate for other causes seems to be lacking, and we recommend at present that this be dictated by the clinical need to establish a diagnosis. Similarly, testing for HIV infection that presents initially as a mononucleosis-like illness in recently infected patients (also known as the acute retroviral syndrome) is indicated only if HIV infection is suspected clinically and if testing is combined with appropriate patient counselling.

UK GMS contract indicator: none.

What tests should I perform for a pregnant woman in contact with a child with a macular rash?
We recommend:

- obtaining history of past rubella vaccination and testing for rubella immunity
- sending serum sample to the laboratory with details of pregnancy and contact, asking for erythrovirus (parvovirus) B19 serology, and rubella serology if necessary

- considering measles serology in patients arriving recently from areas for measles.

The clinical problem here is that a pregnant woman in contact with a non-vesicular rash illness may acquire either rubella or erythrovirus (formerly known as parvovirus) B19 infection, both of which have potential deleterious consequences for pregnancy.[43] Maternal rubella virus infection in the first 12 weeks of pregnancy carries a near 100% risk of the congenital rubella syndrome in the developing fetus. Protean manifestations of this are observed, the most common being cataracts, congenital heart disease and central nervous system abnormalities including sensorineural deafness. Maternal rubella at 12–18 weeks of pregnancy is more likely to lead to single organ damage, usually deafness. Maternal infection with erythrovirus B19 results in an increased risk of spontaneous miscarriage. If the pregnancy survives, maternal–fetal transmission of infection may result in fetal heart failure, presenting as hydrops fetalis (only described in maternal infections before 21 weeks of gestation). There is no congenital parvovirus syndrome—that is, live babies born to mothers with documented gestational parvovirus infection do not have congenital developmental abnormalities.

Rubella and erythrovirus B19 infection in the contact patient, whether a child or an adult, may be clinically indistinguishable, giving rise to non-specific macular rashes, and, in women especially, arthralgia and even frank arthritis that may occur in the absence of a rash. Fewer than half of the women with parvovirus infection had rash or arthralgia.[44] Both infections should therefore be considered in any pregnant woman in contact with a rash illness.

If a pregnant woman in contact with a child (or adult) with a rash illness has had two previous rubella IgG-positive results on record, two documented rubella immunisations, or one IgG-positive result and one documented immunisation, she can be regarded as immune to rubella and reassured that the risk of rubella infection is remote. She should still be investigated for possible erythrovirus B19 infection.[44–46] If none of the above obtains, she should be investigated for both rubella and erythrovirus B19 infection. Note that should a rash develop in the pregnant woman herself, she should be advised to seek medical advice at once.

Laboratory investigation of rubella and erythrovirus B19 infections is by serological testing. Thus, a serum sample should be sent to the laboratory, together with details of the stage of pregnancy, the nature of the contact (particularly the time(s) when the contact took place) and any past rubella IgG testing/vaccination. The laboratory will test the serum for B19 IgG and IgM, and, where indicated, rubella IgG and IgM.[45–47] Further action will depend on the results of these tests, which may identify susceptibility to infection with, immunity to, or evidence of recent infection with, one or both viruses. The laboratory report should provide an interpretation of the results, and clear guidance on the need for, and timing of, further sampling and testing. Good communication between the primary care physician (providing details of pregnancy and contact) and the laboratory (providing interpretation of results and guidance for further testing) is essential.

Although measles is rare in the UK, with increasing travel to parts of the world where it is endemic and also an increase in people arriving from countries where the disease is endemic, this possibility should be considered in such people.

UK GMS contract indicator: none.

CONCLUSION

This seventh review brings to a running total of approximately 86 question-and-answer sets written to provide an overview of current advice in the use of laboratory tests in primary care. Answers to the first six question–answer sets can be found elsewhere.[20 21 48–51] The seven reviews have all used a common search methodology,[52] although where recent systematic reviews have been performed, the guidance relies heavily also on the findings of these reviews. Authors wishing to consult the UK General Medical Services Contract and the current Quality and Outcomes Framework guidance can find these on their resective websites,[53 54] along with the 2006 update.[55]

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REFERENCES

1 **British Committee for Standards in Haematology**. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. *Br J Haematol* 2004;**125**:294–317.
2 **Barnes PW**, McFadden SL, Machin SJ, *et al*. The International Consensus Group for Hematology Review: suggested criteria for action following automated CBC and WBC differential analysis. *Lab Haematol* 2005;**11**:83–90.
3 **CLL Trialists' Collaborative Group**. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomised trials. *J Natl Cancer Inst* 1999;**91**:861–8.
4 **Haddy TB**, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med* 1999;**133**:15–22.
5 **Laksham R**, Finn A. Neutrophil disorders and their management. *J Clin Pathol* 2001;**54**:7–19.
6 **Bhatt V**, Saleem A. Review: drug-induced neutropenia—pathophysiology, clinical features, and management. *Ann Clin Lab Sci* 2004;**34**:131–7.

7 **Boxer L**, Dale DC. Neutropenia: causes and consequences. *Semin Hematol* 2002;**39**:75–81.
8 **Lange RD**. Cyclic hematopoiesis: human cyclic neutropenia. *Exp Hematol* 1983;**11**:435–51.
9 **Moses S**. Medication causes of neutropenia. *Family practice notebook*. http://www.fpnotebook.com/HEM196.htm (accessed 16 Jan 2007).
10 **Spry CJF**. *Eosinophils: a guide to the scientific and medical literature*. Oxford, England: Oxford University Press, 1988.
11 **Rothenberg ME**. Mechanisms of disease: eosinophilia. *N Eng J Med* 1998;**338**:1592–600.
12 **Lombardi C**, Giovanni P. Eosinophilia and disease: clinical revision of 1862 cases. *Arch Intern Med* 2003;**163**:1370–3.
13 **Fauci S**, Harley JB, Roberts WV, *et al*. NIH conference: the idiopathic hypereosinophilic syndrome: clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med* 1982;**97**:78–92.
14 **Brito-Babapulle F**. The eosinophilias, including the idiopathic hypereosinophilic syndrome. *Br J Haematol* 2003;**121**:203–23.
15 **Brigden M**, Graydon C. Eosinophilia detected by automated blood cell counting in ambulatory North American outpatients. *Arch Pathol Lab Med* 1997;**121**:963–7.
16 NHS Scotland Health Technology Assessment 4. The organisation of troponin testing services in acute coronary syndromes. http://www.nhshealthquality.org/nhsqis/files/HTA_march04_web.pdf (accessed 17 Jan 2006).
17 **Collinson PO**, Boa FG, Gaze DC. Measurement of cardiac troponins. *Ann Clin Biochem* 2001;**38**:423–49.
18 **The Joint European Society of Cardiology/American College of Cardiology Committee**. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000;**21**:1502–13.
19 **Collinson PO**, Stubbs PJ. Are troponins confusing? *Heart* 2003;**89**:1285–7.
20 **Smellie WSA**, Wilson D, McNulty CAM, *et al*. Best practice in primary care pathology: Review 1. *J Clin Pathol* 2005;**58**:1016–27.
21 **Smellie WSA**, Forth J, Bareford, et al. Best practice in primary care pathology: Review 3. *J Clin Pathol* 2006;**59**:781–9.
22 **Smellie WSA**. Cases in laboratory medicine. Testing pitfalls and guidance in lipid management. *BMJ* 2006;**333**:83–6.
23 **Thompson GR**. *Secondary hyperlipidaemia, a handbook of hyperlipidaemia*. London: Current Science, 1989:143–59.
24 **National Cholesterol Education Programme**. Detection, evaluation and treatment of high blood cholesterol in adults (Adult treatment panel III) (2001 guideline, 2004 update) http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04.htm (accessed 17 Jan 2007).
25 JBS 2. Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;**91**:1–52.
26 **National Service Framework**. Coronary heart disease. *Preventing coronary heart disease in high risk patients*. London: Department of Health, 2000.
27 **Pignone MP**, Philips CJ, *et al*. Screening and treating adults for lipid disorders. *Am J Prev Med* 2001;**20**:77–89.
28 **National Institute for Clinical Excellence**. *Management of type 2 diabetes: management of blood pressure and blood lipids*. National Institute for Clinical Excellence London, UK: NICE, 2002, http://www.nice.org.uk (accessed 17 Jan 2007).
29 **Birjmohun R**, Hutten B, Kastelein JP, *et al*. Efficacy and safety of high density lipoprotein cholesterol-increasing compounds. *J Am Coll Cardiol* 2005;**45**:185–97.
30 **The FIELD study investigators**. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD Study): randomised controlled trial. *Lancet* 2005;**366**:1849–61.
31 **Sacks FM**, for the Expert Group on HDL Cholesterol. The role of high density lipoprotein (HDL) cholesterol in the prevention and treatment of coronary heart disease: Expert Group recommendations. *Am J Cardiol* 2002;**90**:139–43.
32 **Wei L**, Murphy MJ, MacDonald TM. The impact on cardiovascular events of increasing high-density lipoprotein cholesterol with and without lipid-lowering drugs. *Heart* 2006;**92**:746–51.
33 **Shepherd J**, Betteridge J, Van Gaal L, on behalf of a European consensus panel. Nicotinic acid in the management of dyslipidaemia associated with diabetes and metabolic syndrome: a position paper developed by a European Consensus Panel. *Curr Med Res Opin* 2005;**21**:665–82.
34 **Anderson JP**. Clinical aspects of Epstein-Barr virus infection. *Scand J Infect Dis* 1991;**80**(Suppl):94–104.
35 **Ebell MH**. Epstein-Barr virus infectious mononucleosis. *Am Fam Physician* 2004;**70**:1279–87.
36 **Hoagland RJ**. Infectious mononucleosis. *Prim Care* 1975;**2**:295–307.
37 **Aronson MD**, Kamaroff AL, Pass TM, *et al*. Heterophil antibody in adults with sore throat: frequency and clinical presentation. *Ann Intern Med* 1982;**96**:505–8.
38 **Axelrod P**, Fenestone AJ. Infectious mononucleosis in older adults. *Am Fam Physician* 1990;**42**:1599–606.
39 **Burroughs KE**. Athletes resuming activity after infectious mononucleosis. *Arch Fam Med* 2000;**9**:1122–3.
40 **Linderholm M**, Boman J, Juto P, *et al*. Comparative evaluation of nine kits for rapid diagnosis of infectious mononucleosis and Epstein-Barr virus-specific serology. *J Clin Microbiol* 1994;**32**:259–61.
41 **Evaluations and Standards Laboratory, Centre for Infections**. VSOP 6.2. Epstein-Barr virus serology. http://www.hpa-standardmethods.org.uk/documents/vsop/pdf/vsop6.2.pdf (accessed 17 Jan 2007).
42 **Bruu AL**, Hjetland R, Holter E, *et al*. Evaluation of 12 commercial tests for detection of Epstein-Barr virus-specific and heterophile antibodies. *Clin Diagn Lab Immunol* 2000;**7**:451–6.
43 **Morgan-Capner P**, Crowcroft NS, on behalf of the PHLS Joint Working Party of the Advisory Committees of Virology and Vaccines and Immunisation. Guidelines on the management of, and exposure to, rash illness in pregnancy (including consideration of relevant antibody screening programmes in pregnancy). *Communicable Dis Public Health* 2002;**5**:59–71.
44 **Cartter ML**, Farley TA, Rosengren S, *et al*. Occupational risk factors for infection with parvovirus B19 among pregnant women. *J Infect Dis* 1991;**163**:282–5.
45 **Evaluations and Standards Laboratory, Centre for Infections**. VSOP 32. Investigation of rubella in pregnant women of unknown rubella immunity status exposed to rash illness. http://www.hpa-standardmethods.org.uk/documents/vsop/pdf/vsop32.pdf (accessed 17 Jan 2007).
46 **Evaluations and Standards Laboratory, Centre for Infections**. VSOP 30. Investigation of erythrovirus (parvovirus) B19 in pregnant women exposed to rash illness. http://www.hpa-standardmethods.org.uk/documents/vsop/pdf/vsop30.pdf (accessed 17 Jan 2007).
47 **Evaluations and Standards Laboratory, Centre for Infections**. VSOP 33. Pregnant patient in contact with rash illness. http://www.hpa-standardmethods.org.uk/documents/vsop/pdf/vsop33.pdf (accessed 17 Jan 2007).
48 **Smellie WSA**, Forth J, McNulty CAM, *et al*. Best practice in primary care pathology: review 2. *J Clin Pathol* 2006;**59**:113–20.
49 **Smellie WSA**, Forth J, Sundar S, *et al*. Best practice in primary care pathology: review 4. *J Clin Pathol* 2006;**59**:893–902.
50 **Smellie WSA**, Forth J, Ryder S, *et al*. Best practice in primary care pathology: review 5. *J Clin Pathol* 2007;**59**:1229–37.
51 **Smellie WSA**, Forth J, Coleman JJ, *et al*. Best practice in primary care pathology: review 6. *J Clin Pathol*. Published Online First 5 July 2006 doi: 10, 1136/jcp.2006.040014..
52 **Smellie WSA**, Wilson D, Finnigan DI, *et al*. Best practice in pathology. Methodology for constructing guidance. *J Clin Pathol* 2005;**58**:249–53.
53 **General Medical Services Contract**. www.nhsconfed.org/docs/contract.pdf (accessed 17 Jan 2007).
54 **NHS Confederation**. Quality and outcomes framework. Accompanying guidance document. 2003. NHS Confederation. www.nhsconfed.org/docs/quality_and_outcomes_framework_guidance.pdf (accessed17 Jan 2007).
55 Revisions to the GMS contract 2006/7. http://www.nhsemployers.org/primary/index.cfm (accessed 17 Jan 2007).